DISSERTATION ON

Osteoporosis in Non cholestatic decompensated chronic liver disease and its co-relation with Vitamin D and Parathyroid hormone levels

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CERTIFICATE

This is to certify that the dissertation entitled "Osteoporosis in Non cholestatic decompensated chronic liver disease and its co-relation with Vitamin D and Parathyroid hormone levels" is a bonafide work done by **DR.S.P.S ANANDAN**, post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai-3 in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the Academic period from April 2007 to March 2010.

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DECLARATION

I solemnly declare that the dissertation entitled "**Osteoporosis in Non cholestatic decompensated chronic liver disease and its co-relation with Vitamin D and Parathyroid hormone levels**" is done by me at Madras Medical College, Chennai-3 during April 2008 – March 2011 under the guidance and supervision of Prof.A.Radhakrishnan, M.D., to be submitted to The TamilnaduDr M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE IN GENERAL MEDICINEBRANCH-I.

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ABBREVIATIONS

25(OH) VIT D3	25 HYDROXY VITAMIN D3
PTH	PARATHYROID HORMONE
DEXA	DUAL ENERGY XRAY ABSORP-TIOMETRY
BMD	BONE MINERAL DENSITY
ALD	ALCOHOLIC LIVER DISEASE
Ca	CALCIUM
P	PHOSPHOROUS
AST	ASPARTATE TRANSAMINASE
ALT	ALANINE TRANSAMINASE
ALP	ALKALINE PHOSPHATASE
CLD	CHRONIC LIVER DISEASE
X-RAY LS SPINE	X-RAY LUMBOSACRAL SPINE

CONTENTS

INTRODUCTION

INTRODUCTION

A. Metabolic bone disease

Bone metabolism:

Remodelling of bone continues throughout life in response to mechanical stimuli and other regulatory factors. The normal sequence of bone remodeling involves 4 steps, the first of which is activation of osteoclasts by osteoblasts . The next step is bone resorption, which involves replication of osteoclast precursors and their differentiation, migration and fusion into mature osteoclasts. The third phase begins when the osteoclasts have resorbed most of the mineral and matrix. This is the reversal step or coupling, meaning the reversal from bone resorption to formation, the signal for which is not definitely known . The last step is the formation of new bone by osteoblasts filling the resorption cavity. Mineralization then follows within a few days. This sequence of activation, resorption, reversal, formation and mineralization occurs normally on 10 percent of the bone surface and has a duration of several months. The remodelling process is regulated by circulating hormones and by local factors (Figure 1).

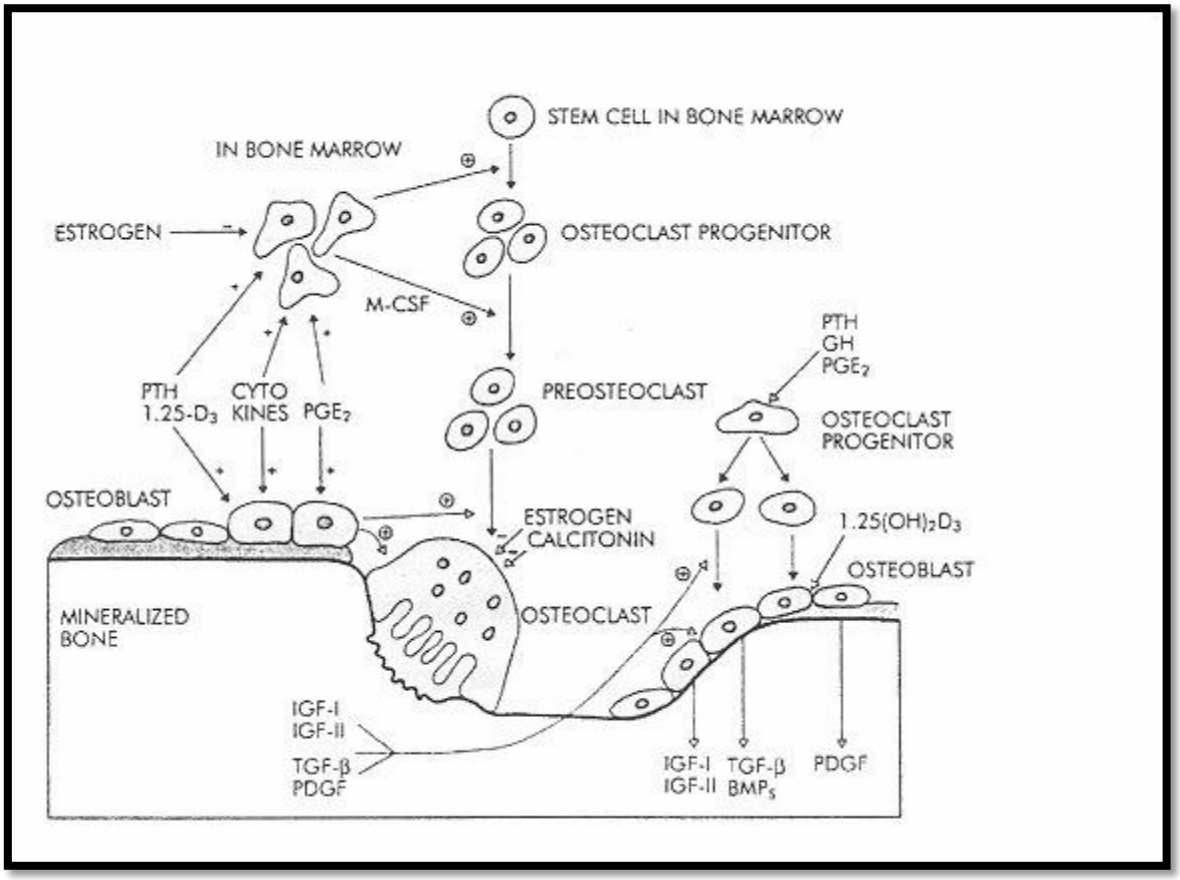


Figure 1. Normal bone remodeling (Ljunghall et al, Doctors Manual, 1995)

Hormones that influence the rate of normal bone remodeling are most notably parathyroid hormone (PTH), vitamin D and calcitonin. Increased PTH levels stimulate bone remodelling by increasing resorption. Vitamin D, as its active metabolite 1,25-dihydroxy vitamin D3 (1,25(OH)2 D3) (the 25 hydroxylation step taking place in the liver), is essential for mineralization of new bone and is also a potent bone resorption agent. The full role of vitamin D in normal bone metabolism is not clearly understood. Other important hormones in bone metabolism are growth hormone (GH), thyroid hormone and sex steroids. Examples of other systemic and local factors affecting osteoblast and/or

osteoclast function are interleukin-1 and -6, transforming growth factor-B(TGF-B) and insulin-like growth factors (IGF). There are two types of bone tissue in adult life, trabecular and cortical bone. Trabecular bone is concentrated in the spine and at the ends of long bones and constitutes about 25% of the total bone mass. The annual turnover rate in trabecular bone is about 25% and in cortical bone about 2-3% making trabecular bone more vulnerable to factors influencing bone metabolism . Bone mass is determined by the peak bone mass achieved around the age of 20-30 and the subsequent gradual loss of bone by about 0.5-1% per year. Bone mass is higher in men than in women throughout adult life, and in women there is an accelerated bone in loss in the first years after menopause at about 2% per year . During the course of their lifetime, women lose about 50% and men 30% of their trabecular bone.

Osteoporosis and osteomalacia:

Osteoporosis and osteomalacia are two forms of metabolic bone disease. Osteoporosis is defined as a systemic disease of the skeleton, characterized by low bone mass and altered micro-architecture of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture . There is a disintegration of the bone matrix with normal ratio

of mineral to matrix . *Primary osteoporosis includes* postmenopausal osteoporosis (type I osteoporosis) and senile osteoporosis (type II osteoporosis) of elderly women and men. Postmenopausal osteoporosis is characterized by increased bone resorption (high bone turnover) due to estrogen deficiency. There is predominantly a loss of trabecular bone with resulting fractures mainly at the vertebrae.

In senile osteoporosis the loss of trabecular and cortical bone is similar due to the combined effects of increased resorption and decreased bone formation (low bone turnover) and is associated with vertebral or hip fractures. Other general risk factors for osteoporosis are low body weight, physical inactivity, smoking, and genetic factors. *Secondary osteoporosis* refers to bone loss caused by a specific defined clinical disorder. Secondary osteoporosis can be either high or low bone turnover osteoporosis depending on the cause.

Table 1. Causes of secondary osteoporosis in adults

Endocrine/metabolic	**Drugs**
Hypogonadism	Glucocorticosteroids
Hyperadrenocorticism	Chronic heparin administration
Thyrotoxicosis	Anticonvulsants
Systemic mastocytosis	
Nutritional	**Other**
Malabsorption/malnutrition	Osteogenesis imperfecta
Chronic liver disease	Ehler-Danlos syndrome
Vitamin D deficiency	Marfan syndrome
Anorexia nervosa	Myeloma
Alcoholism	Immobilization/space flight
Gastric surgery	

Osteomalacia is rare in developed countries but is characterized by impaired mineralization of bone matrix, most often due to vitamin D deficiency. Biochemical abnormalities are common in osteomalacia but the diagnosis is best established by use of transiliac bone biopsy in combination with the use of timed tetracycline. The histological examination of the undecalcified bone shows an increase in the amount of unmineralised osteoid and depressed rate of bone formation.

Measurements of bone mineral density:

Bone mineral density (BMD;g/cm2) is measured by non-invasive methods based on radiology. A specified amount of electromagnetic energy, in the form of a Gamma or X-ray beam, is sent through a region of interest and the amount exiting is quantified by a detector. Single photon absorptiometry (SPA), introduced in the 1960s measures BMD reliably only at peripheral sites, having small amounts of surrounding tissue, such as the heel and the wrist. Dual-energy X-ray absorptiometry (DEXA) was introduced in the late 80-ies and is now the most widespread technique for evaluating BMD in patients at risk of osteoporosis. With DEXA, two distinct energy levels are used to resolve contributions from soft tissue and bone making it possible to measure

BMD at central sites such as the spine and the proximal femur. The precision error for DXA is about 1-2% which is important when estimating bone loss in longitudinal studies. If expected bone loss is of the same order, i.e. 1-2% per year, measurements should be performed with not less than1-2 year's interval. Since 1994 the World Health Organization (WHO) has recognized a working definition where osteoporosis is defined as a BMD value of 2.5 SDs below the mean for healthy young women (**Table 2**). No such generally accepted definition of osteoporosis exists for men at the present.

Table 2.World Health Organization (WHO) working definition.

Bone mineral density Classification

Above –1 SDNormal

Between –1 SD and –2.5 SD Low bone mass or osteopenia

Below –2.5 SD Osteoporosis

Below –2.5 SD and fractures Severe osteoporosis

The comparison with the mean BMD for young adults of the same sex is termed the *Tscore* and is expressed as the number of standard deviations from the reference group mean value. Thus, according to the WHO´s definition, a woman with a T-score below–2.5 has osteoporosis.

In clinical practice the use of T- scores has also been adopted for men. A *Z-score* is the number of standard deviations from age-matched and weight adjusted reference population of the same sex.

B. Metabolic bone disease in chronic liver disease

Chronic liver disease:

Chronic liver disease (CLD) can be classified into diseases with primarily *hepato-cellular* damage and *cholestatic* diseases. Examples of hepato-cellular CLD are autoimmune *chronic* hepatitis (AICAH), chronic viral hepatitis B and C and alcoholic liver disease. Autoimmune CAH is a disease of unknown etiology, has a prevalence of about 5-10/100.000. It occurs mainly in young women (sex ratio 8:1) and is treated with longterm corticosteroid therapy. Alcoholic liver disease includes steatosis, which is reversible upon abstinence, alcoholic hepatitis and cirrhosis. Alcohol is the most common cause of liver cirrhosis in India.

Liver failure and the Child-Pugh classification:

The final stage of chronic inflammation in the liver is cirrhosis. Liver cirrhosis gives rise to portal hypertension and complications such as bleeding due to esophageal varices, ascites and encephalopathy. Hepato-cellular failure results in hyperbilirubinemia, hypoalbuminemia and prolonged prothrombin time. Child´s grade is used to assess

hepatocellular function in cirrhosis based on these factors. The Child-Pugh classification is a modified grading system shown to be reliable in predicting survival of patients presenting with variceal bleeding but is also widely used as a method of assessing liver function (**Table 3**).

Table 3. Child-Pugh classification of hepatic functional reserve in cirrhosis

ASSESSMENT CRITERA	POINTS SCORED		
	1	2	3
ENCEPHALOPATHY	NONE	1-2	3-4
ASCITES	NONE	SLIGHT	MOD
BILIRUBIN(mg/dl)	<2	2-3	>3
ALBUMIN(g/dl)	>3.5	2.8-3.5	<2.8
PROTHROMBIN TIME(INR)	<1.7	1.7-2.2	>2.2

CLASS A: 5-7; CLASS B: 8-9; CLASS C: 10-15

Hepatic Osteodystrophy:

In 1939 a 69 year old woman with long-standing intrahepatic obstructive jaundice and spinal osteoporosis with vertebral compressions was described . Since then it has been firmly established that chronic cholestasis, and also other forms of CLD, are associated with metabolic bone

disease. In the era of liver transplantation, metabolic bone disease complicating CLD has become a major clinical problem. After liver transplantation the combination of high dose corticosteroids and immobilization accelerates bone loss leading to a high post-transplant fracture rate ranging from 17-65%. Decreased BMD pre-transplant, however, is a major risk factor for the development of post-transplant fracture .The term "hepatic osteodystrophy" covers both osteomalacia and osteoporosis.Steathorrhea with malabsorption of fat-soluble vitamins, including vitamin D, accompanies symptomatic cholestatic liver disease. Therefore osteomalacia might be expected to complicate CLD, as in fact was reported in earlier studies [36-37].

But over the last two decades, better histomorphometric techniques (including double-Tetracycline labeling for diagnosing osteomalacia) have made it clear that the main bone abnormality in CLD, cholestatic or hepato-cellular, is osteoporosis and that osteomalacia is very rare. Most histomorphometric studies have found osteoporosis in CLD to be of a low bone turnover type with reduced osteoblast function, and measurements of biochemical markers of bone metabolism, such as osteocalcin, have confirmed these findings .

The pathogenesis of osteoporosis in CLD is unknown. Advanced liver disease and cirrhosis are associated with an increased prevalence of osteoporosis . The way in which liver failure affects osteoblasts and contributes to the development of osteoporosis is unclear. Numerous growth factors, some of which affect osteoblast function, such as IGF-l and TGF-β, are synthesized by the liver.

Toxic substances, such as aluminium and copper, which accumulate in liver failure might also affect bone metabolism. In haemochromatosis an increased iron burden might impair osteoblastic activity . Bilirubin has been shown to inhibit osteoblast proliferation in vitro . Whether cholestasis per se is a risk factor for osteoporosis in CLD is uncertain. Cholestatic CLD has traditionally been considered to be associated with osteoporosis more than other types of CLD and most studies of metabolic bone disease in CLD involve women with PBC. In pre-transplant patients suffering from different liver disorders, the highest prevalence of metabolic bone disease was found in patients with PBC and PSC. Other studies, however, have reported similar prevalence rates for osteoporosis in patients with hepato-cellular CLD as in patients with cholestatic CLD, ranging from 9 to 53% . Low levels of serum vitamin D3 metabolites and calcium malabsorption are found in CLD .

Whether vitamin D deficiency is associated with metabolic bone disease in CLD is uncertain.

1 ,25-dihydroxyvitamin D [1,25$(OH)_2$D] is the major steroid hormone involved in mineral ion homeostasis regulation. In response to ultraviolet radiation of the skin, a photochemical cleavage results in the formation of vitamin D from 7-dehydrocholesterol. Vitamin D from plant sources is in the form of vitamin D_2, whereas that from animal sources is vitamin D_3. Vitamin D enters the circulation, whether absorbed from the intestine or synthesized cutaneously, bound to vitamin D–binding protein, an alpha-globulin synthesized in the liver. Vitamin D is subsequently 25-hydroxylated in the liver by cytochrome P450–like enzymes in the mitochondria and microsomes. The second hydroxylation, required for the formation of the mature hormone, occurs in the kidney. Since one of the essential steps of Vitamin D3 formation occurs in the liver this process may be affected in chronic liver disease. Further there may be impaired absorption and reduced enterohepatic circulation in patients with chronic liver disease. Vitamin D insufficiency leads to compensatory hyperparathyroidism and this is an important risk factor for osteoporosis and fractures. Vitamin D inadequacy may also affect risk and/or severity of other diseases including cancers (colorectal/prostate/breast), autoimmune diseases and diabetes.

So Vitamin D may play an important role in causing metabolic bone disease in chronic liver disease patients. The aim of this study is to find out the 25(OH) vitamin D3 and parathyroid hormone disturbances that occur in chronic liver disease patients so that their role in causing bone disease can be established. It may open up other treatment options like vitamin D supplementation. Further their levels are correlated with the severity of liver disease calculated as per Child Pugh scoring system.

Hyperparathyroidism, despite vitamin D replacement, has been described in PBC .Others have not found evidence of hyperparathyroidism in patients with CLD .Treatment with corticosteroids and hypogonadism in men and women are reported by some as risk factors for osteoporosis in CLD. Others have not found treatment with corticosteroids to be associated with low BMD in CLD. Other general factors in patients with CLD such as alcohol consumption, low body weight and physical inactivity have not been reported as independent risk factors for osteoporosis in CLD but can be assumed to be important.

Potential pathophysiological factors in osteoporosis in chronic liver disease

Lack of growth factors produced by the liver

Accumulation of toxins

Cholestasis

Hyperbilirubinemia

Vitamin D deficiency

Vitamin K deficiency

Calcium deficiency

Hypogonadism

Treatment with corticosteroids

Alcohol consumption

Low body weight

Physical inactivity

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

1.To determine the prevalence of osteoporosis in patients with Decompensated chronic liver disease ,

2. To analyse the relationship of Vitamin D and Parathyroid hormone levels to osteoporosis in these patients.

3.To evaluate other risk factors that may contribute to osteoporosis in patients with Chronic Liver Disease

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

Chronic Liver disease is a common problem that is associated with increased mortality and poorer health-related quality of life, regardless of the underlying etiology. One of the morbidities associated with chronic liver disease is metabolic bone disease. There is an increased incidence of both osteomalacia and osteoporosis in patients with chronic liver disease.

Prevalence and Clinical Importance:

The reported prevalence of osteoporosis among patients with chronic liver disease ranges from 20% to 100%, depending on patient selection and diagnostic criteria. The pathogenesis is unclear and likely is multifactorial. Regardless of the etiology of bone disease in these patients, they have an increased incidence of bone pain and fractures, a major source of morbidity. There is also a further significant increase in the risk of fractures following liver transplantation for end stage chronic liver disease.

OSTEOPOROSIS AND BONE MINERAL DENSITY:

Definition and diagnosis of osteoporosis

The definition of osteoporosis is centered on measurement of bone mineral density (BMD) and identifies the majority of patients who will sustain a fracture in the future. It is defined in women as a BMD in the hip and/or spine that is 2.5 standard deviations (SDs) or more below the young adult mean value (T score less than −2.5). A similar cut off may be used in men although the evidence to support this is less secure than in women. Osteopenia is defined as a T score between −1 and −2.5. Although a T score is used to define osteoporosis (World Health Organization, 1994) BMD can also be compared with age matched controls. A z score of −2 defines a BMD 2 SDs below the mean value of age matched controls.

Relationship between BMD and fracture risk

Prospective studies have shown that the risk of fracture increases progressively with decreasing BMD, the risk of fracture increasing two to threefold for each SD decrease in BMD.[4] BMD has a high specificity for fracture but a low sensitivity and so has not been advocated for population screening.

Measurement of bone mineral density

Bone density can be measured at a number of skeletal sites, including the lumbar spine and femoral neck, using dual energy *X* ray absorptiometry (DEXA). Lumbar spine measurements are unreliable in the elderly due to the presence of osteophytes, extra skeletal calcification, and vertebral and/or spinal deformity. Ultrasound measurements of the os calcis have been shown to predict fracture risk in postmenopausal women but diagnostic thresholds have not been established and so this cannot yet be recommended in clinical practice.

Clinical risk factors

Bone mass increases through childhood reaching a peak in the third decade and then after 40 years declines in both sexes but more rapidly in women, accelerating after the menopause. Peak bone mass is determined by genetic factors, hormonal status, diet, and exercise, and men have a higher peak bone mass than women. Thus irrespective of other factors, the incidence of osteoporosis increases in the elderly as age related bone loss is a normal phenomenon.

The risk of fracture is determined not only by bone density but also by trabecular architecture, skeletal geometry, bone turnover, and

non-skeletal risk factors such as postural instability and the propensity for falls.

Risk factors for osteoporosis and subsequent fracture, irrespective of the presence of chronic liver disease, include low body mass index (<19 kg/m^2), alcohol excess, prolonged corticosteroid therapy (prednisolone 5 mg/day for more than three months), physical inactivity, previous fragility fracture, *early* maternal hip fracture (<60 years), hypogonadism, and premature menopause (age <45 years).

When assessing the risk of osteoporosis in individuals with liver disease it is important to realize that these patients often have a low body mass index, may drink excessive amounts of alcohol, and may be receiving corticosteroids. Certain liver diseases such as primary biliary cirrhosis occur predominately in postmenopausal women and cirrhosis is more prevalent with increasing age.

Biochemical markers of bone disease:

There is an association between bone turnover and fracture risk, independent of BMD.

Biochemical markers of bone turnover can be divided into two groups: markers of resorption and markers of formation. The principal markers of bone formation are the procollagen propeptides of type 1

collagen, osteocalcin, and the bone isoenzyme of alkaline phosphatase. The latter is less useful in chronic liver disease as it is difficult to measure accurately in the presence of high values of liver alkaline phosphatase.

The most widely used markers of bone resorption are: urinary excretion of deoxypyridinoline, pyridinoline, and type 1 collagen cross linked N-telopeptide. These are usually expressed in relation to urinary creatinine. Urine hydroxyproline is a poor marker and now rarely used.

These serum bone markers may prove useful in assessing response to treatment in the future in individuals without chronic liver disease. However, as the levels are affected by the extent of hepatic fibrosis and none of these markers has been studied in patients with chronic liver disease, they cannot yet be recommended as a means of assessing bone loss and the risk of fracture in cirrhotic patients.

PATHOGENESIS OF BONE LOSS IN CHRONIC LIVER DISEASE

Osteoporosis

Bone loss occurs as a result of increased bone turnover and/or remodeling imbalance. The latter may be due to reduced formation or increased resorption or a combination of the two. Some studies have shown increased bone resorption, even in the absence of osteoporosis, in the pres-

ence of chronic liver disease whereas most others have shown decreased bone formation.[5,6]

Osteomalacia

Osteomalacia can also lead to low BMD. The classical biochemical changes are hypocalcaemia, hypophosphatemia, increased parathyroid hormone, and elevated bone alkaline phosphatase although serum calcium and phosphate are often normal. Hepatic osteomalacia, as defined by strict histomorphometric criteria, is rare.[7, 8] .In a recent study of 60 patients awaiting liver transplantation none had evidence of osteomalacia on bone biopsy (J E Compston, personal communication).

Vitamin D deficiency/insufficiency

Vitamin D is obtained from endogenous skin synthesis which involves exposure to sunlight, leading to the production of cholecalciferol (vitamin D_3). Ergocalciferol (vitamin D_2) and vitamin D_3 are also acquired from natural and fortified food. Vitamin D undergoes 25 hydroxylation in the liver which is only impaired in the presence of severe chronic liver disease. Vitamin D insufficiency is associated with secondary hyperparathyroidism, increased bone turnover, and accelerated bone loss. As vitamin D deficiency becomes more severe, impaired bone

mineralisation leads to accumulation of osteoid which is a feature of osteomalacia.

Many studies have shown low serum levels of 25-hydroxyvitamin D in patients with chronic liver disease[9,10] and levels fall with disease progression in cirrhosis.[11] Although malabsorption of 25-hydroxyvitamin D has been demonstrated in patients with chronic liver disease, this does not completely account for the low vitamin D levels seen in these patients. It is likely that both reduced exposure to UV light and dietary insufficiency account for vitamin D deficiency in the majority of cases. There is also impaired cutaneous synthesis of vitamin D in the presence of jaundice.

Prevalence of osteoporosis and fracture

There are no prospective studies addressing the fracture rate in patients with chronic liver disease and no good observational studies. Many studies have investigated the prevalence of osteoporosis, as defined by BMD measurements. However, in these studies different methodologies and different sites were used to assess BMD. The definition of osteoporosis also differed between studies and patients were selected using different criteria.

Patients with chronic liver disease also have other risk factors for osteoporosis related to their disease, such as hypogonadism, vitamin D insufficiency, excess alcohol consumption, corticosteroid use, and low body mass index. The proportion of patients with these risk factors also varies between studies.

Cirrhosis

Osteoporosis and fractures are more common in cirrhotics than in the normal population in the absence of confounding risk factors such as female sex, cholestasis, and excess alcohol. In a study of male cirrhotics with a viral etiology, half of the 32 patients were osteoporotic, defined as a T score of less than −2.5 at the lumbar spine or femoral neck. The mean Z score at the lumbar spine was −1.27 (1.6) g/cm^2, indicating the wide inter individual variation in bone density even among this relatively homogeneous population of cirrhotics[2] .In another study of 74 males with hepatitis B or C cirrhosis, osteoporosis in the lumbar spine, defined as a z score of less than −2, was seen in 20% and fractures in 6.7%, mean BMD being significantly lower than in healthy controls.[12] The prevalence of osteoporosis is related to the severity of liver disease in cirrhosis.[6,13]In a study of 58 cirrhotic patients referred for liver transplantation, 43% had osteoporosis, defined by at least one vertebral fracture and/or a lumbar spine BMD more than 2 SDs below the mean value for normal subjects of

the same age (z score <−2.0). Alcoholics and those with more severe liver disease—that is, Child Pugh class C patients—had the lowest BMD.[13]

Cholestatic liver disease: A high prevalence of osteoporosis has also been reported in individuals with cholestatic liver disease.

Primary biliary cirrhosis: Many studies have evaluated BMD in patients with primary biliary cirrhosis (PBC).[14-21] It is not clear whether osteoporosis occurs in early stage PBC where there is cholestasis without significant hepatic fibrosis. However, reduction in BMD is related to the severity of liver disease.[14-16]

Not all patients with PBC will develop osteoporosis and the rate of bone loss varies between patients. In 25 patients with PBC and low BMD (z score <−2), spinal BMD fell by 3.5% over a six month period[17] whereas in another study, 210 women with PBC with a range of bone densities, mean rate of bone loss was 2%/year.[16] In a study of 36 PBC patients who were not osteoporotic (defined as lumbar spine BMD >0.800 g/cm^2) at the start of a three year follow up, 11 subsequently became osteoporotic and had a higher annual bone loss than the other 25 patients.[19] In contrast, in a retrospective study of 225 patients with PBC, following on from an earlier study,[22] of the 46% with late stage disease (stage 3/4) who had repeated BMD measurements, only one patient developed osteoporosis (defined as a z score <−2) during a mean follow up

of 10 years (D Jones, personal communication). In contrast with osteoporosis, osteomalacia is rarely seen in PBC.[20]

Other factors that have been associated with osteoporosis in PBC include disease duration and degree of cholestasis, the latter reflecting the stage of liver disease. In a small study of 20 PBC patients, seven (35%) of whom were osteoporotic, osteoporosis was associated with longer duration of disease, intestinal calcium malabsorption, and postmenopausal state.[18]

Although studies have suggested that cholestasis itself is a risk factor for osteoporosis, this may just be a reflection of the coexistence of cirrhosis with severe cholestasis as ursodeoxycholic acid, which improves cholestasis, has no effect on BMD. In a study of 88 female PBC patients, 50 treated with ursodeoxycholic and 38 controls, there was no overall change in BMD in either group over a three year period.[15]

Primary sclerosing cholangitis

Individuals with primary sclerosing cholangitis (PSC) have multiple risk factors for osteoporosis. Patients may be cirrhotic as well as cholestatic and may also have been taking corticosteroids for many years for coexistent inflammatory bowel disease.

In a study of 81 patients with PSC followed up for five years, overall BMD of the lumbar spine was lower than age and sex matched controls.[23] Those patient who had fractures were older, had a longer duration of inflammatory bowel disease, and more advanced liver disease. The incidence of osteoporosis (defined as a T score <−2.5) increased with worsening liver disease and 40% were osteoporotic at the time of liver transplantation and so at increased risk of post-transplant fracture.

Non-cholestatic non-cirrhotic liver disease

The prevalence of osteoporosis in non-cirrhotic liver disease patients who are not cholestatic or hypogonadal is unknown. Studies that have included such patients suggest that cirrhosis is the major independent risk factor for osteoporosis and fracture.

In a study of 115 patients with chronic liver disease, of whom 20% were cholestatic, 36% alcoholic, 52% cirrhotic, and 18% on more than 7.5 mg/day of prednisolone, 29% were found to have osteoporosis, defined as a Z score of less than −2. Mean age of the patients was 49 years (range 20–70). Between 12% and 18% had spinal fractures and peripheral fractures were more common among alcoholics. Both fractures and osteoporosis were more common in cirrhotics than non-cirrhotics and hypogonadal patients. Multiple regression analysis showed age, cirrhosis,

and hypogonadism to be predictive of osteoporosis in the lumbar spine. Hypogonadism, low BMD, and severity of liver disease were predictive of spinal fracture.[24]

In a further study of 133 individuals with chronic liver disease, 24% alcoholic and 36% cirrhotic, the prevalence of lumbar spine osteoporosis varied between 16% and 50% (defined as a z score of less than −2). The highest rates were observed in cirrhotics and PSC patients. In a group of 19 non-cirrhotic patients with chronicactive hepatitis, 21% were osteoporotic but 50% of the group were taking corticosteroids.[25]

Alcohol

Alcohol is an independent risk factor for osteoporosis, alcoholism being associated with a 2.8-fold increase in the risk of hip fractures. In men, excess alcohol, irrespective of cirrhosis or low testosterone levels, is a risk for osteoporotic fractures.[29-36] In a study of 76 men drinking more than 27 units/day for more than 24 years, only 22% of whom had abnormal hepatic histology, lumbar spine BMD was lower than in age matched controls. Thirty per cent had vertebral compression fractures although only 4% were symptomatic.[34] In a further study of 58 male non-cirrhotic drinkers, osteopenia was seen in 23% drinking >10 units/day and cumulative alcohol intake was inversely related to BMD.[35] In women,

excess alcohol in the absence of hypogonadism and cirrhosis is not associated with osteoporosis.[36]

MANAGEMENT

Introduction

There are only a few small randomised controlled trials examining the role of intervention in preventing osteoporosis and reducing subsequent fractures in chronic liver disease. Most of the studies are 1–3 year intervention studies in patients with PBC, not all of whom were cirrhotic. None of the studies was adequately powered to assess reduction in fracture rate as an end point .

Calcium and vitamin D

In elderly women living in sheltered accommodation, combined calcium and vitamin D supplementation reduces the risk of hip and other non-vertebral fractures.

The role of calcium and vitamin D in preventing osteoporosis and fracture in chronic liver disease is unclear. In a cross sectional study of 55 patients with PBC who were all taking adequate dietary calcium and vitamin D or who had been supplemented if deficient, mean BMD was 8% lower than in age and sex matched controls.[14] In another small retrospective study in PBC, vitamin D_3 and calcium supplementation did

not lead to a significant increase in BMD over baseline in the treated group.[42] In the absence of larger studies on the effect of vitamin D supplementation on BMD it seems reasonable to recommend correction of vitamin D insufficiency with an oral daily dose of 800 IU of *vitamin* D_3 and 1 g of calcium.

Osteomalacia has been shown to respond to treatment with oral or parenteral vitamin D or oral alfacalcidol.[46] The role of high dose vitamin D in preventing osteoporosis and fractures is unclear and the efficiency of vitamin D absorption in the setting of chronic liver disease has been poorly studied. However, in one non-randomised controlled study in alcoholic cirrhotics with low BMD and low serum levels of 25 hydroxyvitamin D, oral supplementation with 50 000 IU of vitamin D_2 or 20–50 μg of 25-OH vitamin D did increase BMD over baseline values in the treated group.[10]

Hormone replacement therapy

HRT is given as sequential combination therapy, continuous combination therapy, or oestrogens alone in women who have had a hysterectomy. In patients with chronic liver disease HRT can be given safely.[47,48] It should be given, where possible, via the transdermal route as physiological blood oestrogen levels can be achieved without exposing the liver to high levels of conjugated oestrogens. Transdermal oestradiol should

be used at a dose of 50 μg/day, equivalent to 2 mg daily of oral oestradiol. Unopposed oestrogens can be given to patients who have had a hysterectomy. Sequential or continuous combination therapy of oestrogens followed by progestogen should be given to women who have a uterus as this protects against endometrial hyperplasia. In women who cannot tolerate monthly bleeding, continuous combination therapy can be given providing that the patient has been free of bleeding for a year and is aged over 51 years.

In general, in those women in whom it is indicated, the recommended duration of HRT is 5–10 years. However, the risk of osteoporosis in chronic liver disease continues beyond 10 years and the optimal duration of therapy has not been defined. The decision to continue HRT beyond 10 years has to be made on an individual basis in view of the increased risk of breast carcinoma after 5–10 years of therapy.

In individuals with secondary amenorrhea, for example patients with autoimmune chronic active hepatitis, hypogonadism can be treated using the oral contraceptive pill or combination HRT. The former contains ethinyl oestradiol which is less degradable than oestradiol and so may be more hepatotoxic.

HRT in postmenopausal women without chronic liver disease has been shown to increase BMD in the lumbar spine and other sites.[49] Observational studies, which may overestimate the benefits of HRT, show that oestrogen, also lowers the rate of veterbral and non-vertebral fractures in osteoporotic postmenopausal women.[50] There are also a few small prospective studies showing that HRT reduces vertebral and non-vertebral fracture.[51-54]

Few studies have examined the effect of HRT on BMD and fracture rates in postmenopausal or hypogonadal women with chronic liver disease. In a small retrospective study of 16 postmenopausal patients with PBC, oestrogen replacement resulted in a significant increase in BMD compared with untreated patients at one year and there was no evidence of worsening cholestasis.[42] Long term controlled studies are needed to assess the effect of HRT on BMD and fracture rates in hypogonadal women with chronic liver disease.

Testosterone

Testosterone replacement in hypogonadal men without chronic liver disease leads to increases in BMD.[55] The role of testosterone in eugonadal men is still under evaluation. In a small study of 23 men with fractures, testosterone given for six months resulted in an increase in spinal BMD.[56] In a trial of testosterone in patients with corticosteroid

induced osteoporosis, some of whom were hypogonadal, there was also a significant increase in spinal BMD.[57]

There are no studies of the effects of testosterone replacement in patients with chronic liver disease on BMD and the subsequent fracture risk. Although hypogonadism is reported in male cirrhotics with chronic liver disease and male patients with end stage liver disease being assessed for liver transplantation, the overall prevalence is unknown.[12,13,58]

In patients with chronic liver disease an increase in testosterone binding globulin levels may occur and total serum testosterone levels may overestimate free testosterone. Total testosterone should therefore be expressed in relation to testosterone sex hormone binding globulin (SHBG) levels *if free testosterone levels cannot be measured.*

One concern about restoring testosterone levels to normal in cirrhotics is that this might increase the risk of hepatocellular carcinoma. Cirrhotics have relatively high oestrogen levels and male sex is a major risk factor for hepatocellular carcinoma. As the relative risk of inducing hepatocellular carcinoma in relation to testosterone levels is not known, the potential risk/benefit must be discussed with individuals before starting replacement therapy. Transdermal testosterone is the preferred route of administration in cirrhotic patients as it leads to stable testosterone concentrations within the normal range, therefore avoiding

exposure of the liver to the high levels seen with oral preparations, depot injections, or implants.

Bisphosphonates

Bisphosphonates include oral alendronate, cyclical etidronate, and risedronate. In postmenopausal women with osteoporosis without liver disease, bisphosphonates increase BMD and decrease the incidence of vertebral and non-vertebral fractures.[59] There are no comparative studies comparing the different preparations. Oral alendronate, which can be given as a daily dose of 10 mg or as a 70 mg dose weekly, may cause oesophageal ulceration and so should be avoided in patients with cirrhosis who may have portal hypertension and oesophageal varices because of the potential to precipitate a variceal haemorrhage. No adverse effects on the oesophageal mucosa have been reported with risedronate in clinical trials although post marketing data are not yet available.[60]

Cyclical etidronate has been given safely for up to seven years. However, there is some theoretical concern about the use of long term bisphosphonates as although they increase BMD they may also increase bone mineralisation with potential adverse effects on bone strength.

Bisphosphonates are also effective in preventing corticosteroid induced osteoporosis in patients with PBC. In a randomised placebo

controlled trial of 12 patients with late stage PBC who were given 10 mg of prednisolone for >1 year and who had normal z scores at baseline, cyclical etidronate prevented the fall of 3 SD in BMD which was seen in untreated patients.[37]There are no long term studies of bisphosphonates in preventing fractures in individuals with chronic liver disease.

Bisphosphonates should be taken on an empty stomach in the morning, 0.5–2 hours before consumption of food and other drugs, and at a different time to calcium supplements as calcium binds and inactivates bisphosphonates.

Anabolic steroids

These drugs can cause abnormal liver biochemistry and should be avoided in patients with chronic liver disease

Combination therapies

The role of combination therapy in managing postmenopausal osteoporosis is a current area of interest. In a small non-randomised controlled study of patients with PBC, whose lumbar spine BMD was less than 0.8 g/cm^2, three years of treatment with 0.5 μg daily of calcitriol (1, 25 dihydroxyvitamin D), 1.5 g of calcium, and 40 Medical Research Council units of carbocalcitonin, given subcutaneously three times a week, resulted in an improvement in bone density in the treated group compared with baseline values.[19]

MATERIALS

AND

METHODS

MATERIALS AND METHODS

Study Design:

Cross-Sectional Study.

Study Population:

55 patients with decompensated non cholestatic chronic liver disease (Alcohol and Hepatitis B and C as primary etiology) of any age group and of either sex admitted in medical ward in GGH, Chennai were taken into study irrespective of their primary complaints. The study was done from May 2010 to September 2010.

Inclusion Criteria:

Patients with decompensated chronic liver disease with Alcoholic liver disease and Hepatitis B and C as the primary etiology. Chronic liver disease is defined as liver disease with duration of atleast 6 months and with a diagnosis based on biochemical, serological and histopathological investigations.

Exclusion Criteria:

Patients with decompensated chronic liver disease with impaired renal function and postmenopausal women and those with cholestatic liver disorders.

Ethical Clearance:

Obtained.

Informed Consent:

Obtained from all patients.

Methodology:

A total of 55 patients were identified according to the above criteria and were included in the study.

A questionnaire prepared noted the age, sex, address, primary complaints, jaundice, abdominal distension, swelling of legs, altered sensorium, hematemesis, melena ,easy fatiguability, fever, skin rash ,altered sleep pattern ,loss of weight and appetite and decreased urine output and presence of dyspnea and abdominal pain. Other relevant history like history of drug intake, past medical history, personal history and sexual history was obtained.

Clinical examination included a detailed examination from head to foot, examination of cardiac, respiratory, GI tract, and nervous system. Per rectal in both male and female patients and pelvic examination in females was done.

Laboratory Investigations:

The following investigations are done in all patients during their first visit:

Serum urea, creatinine

Blood sugar,

Complete blood count, including red cell indices, ESR,

Liver function test,

PT/INR,

chest X-ray,

ECG,

USG – Abdomen,

UGI Scopy,

HbsAg,

Anti-HCV,

Serum calcium,

Serum phosphorous,

Serum Vitamin D3,

Parathyroid hormone,

DEXA BMD Value,

In selected patients the following investigations were done for the diagnosis

Liver biopsy.

Table 5:

S.NO	**Parameter**	**Method**
1.	Complete blood count	Automated flow cytometry
2.	ESR	Westegren method
3.	urea	GLDH/urease
4.	creatinine	Picrate method
5.	Serum albumin	Bromocresol green
6.	bilirubin	Calorimetric endpoint diazo
7.	Total protein	Biuret method
8.	Intact PTH	Chemi luminescent Immuno Assay
9.	25-OH VITAMIN D3	Bidirectionally interfaced Chemi Luminescent Immuno Assay
10.	Serum calcium	Photometry assay
11.	Serum phosphorous	Enzyme linked immunosorbent assay
12.	ANA	Enzyme linked immunosorbent assay
13.	HBsAg	C.L.I.A
14.	Anti HCV	ELISA

Measurements of bone mineral density

Bone mineral density (BMD; g/cm2) of the lumbar spine was measured by dual Energy X-ray absorptiometry (DXA)at baseline.BMD was expressed as Score. The WHO´s definition for osteoporosis was applied to classify individuals as either osteoporotic or not.

Statistical Analysis:

SPSS 13 and Excel were used for statistical analysis. Univariate analysis was done with Fisher's exact test and Chi square test for discrete variables and Wilcoxon rank sum test for continuous variables. Logistic regression analysis was done for the risk factors which were found to have a statistically significant association by Univariate analysis to find the independent risk factors associated with osteoporosis.

Limitations:

Small number of study subjects especially females

Chronic liver disease patients only with Alcoholic liver disease and hepatitis B and c were selected for the study.

Conflicts of interest:

None

Table 6:

NORMAL VALUES

Hemoglobin	M: 13.3 – 16.2gms%	F: 12.0 – 15.8gms%
PCV	M: 38.8 – 46.4	35.4 – 44.4
Total Count	3.54 – 9.06x $10^3/mm^3$	
Platelet Count	165 – 415 x $10^3/mm^3$	
MCV	80 – 100 Fl	
MCHC	32.3 – 35.9g/dL	
MCH	26.7 – 31.9 pg/cell	
ESR	M: 0 -15mm/hr	F: 0-20mm/hr
Reticulocyte count	M: 0.8 – 2.3%	F: 0.8 – 2.0 %
Creatinine	M: 0.6 – 1.2mg/dl	F: 0.5 – 0.9mg/dl
BUN	7 – 20 mgs/dl	
Total Bilirubin	0.3 – 1.3 mgs/dl	
Direct Bilirubin	0.1 – 0.4 mgs/dl	
SGOT	12 – 38 U/L	
SGPT	7 – 41U/L	
Se.Alkaline phosphatase	33 – 96 U/L	
Total Protein	6.7 – 8.6 gms/dl	
Se.Albumin	3.5 – 5.5 gms/dl	
PTH	15-65 pg/ml	
25 OH VITAMIN D3	11.1-42.9 ng/ml	
Serum calcium	8.7-10.2 mg/dl	
Serum phosphorous	2.5-4.3 mg/dl	

RESULTS

AND

OBSERVATIONS

RESULTS & OBSERVATIONS

STUDY POPULATION CHARACTERISTICS:

Among 55 patients included in our study, 41 (74.54%) patients were male, and 14(25.45%) patients were female.

The Mean Age of the patients included in the study is 50.16 mean years, with S.D. of 11.79 years, with Mean Age of males being 51.73 years and females were 39.35 years.

TABLE-7: AGE AND SEX DISTRIBUTION OF STUDY POPULATION

Age Group	Males	Females	Total	Percentage
20-30	0	3	3	5.45%
30-40	3	2	5	9.09%
40-50	12	9	21	38.18%
50-60	14	0	14	25.45%
60-70	11	0	11	20.00%
Above 70	1	0	1	1.82%
Total	41	14	55	100.00%

Most of our patients are in the age group are in the range of 40-50 years age group, and most are males owing to increased prevalence of alcoholism among males .

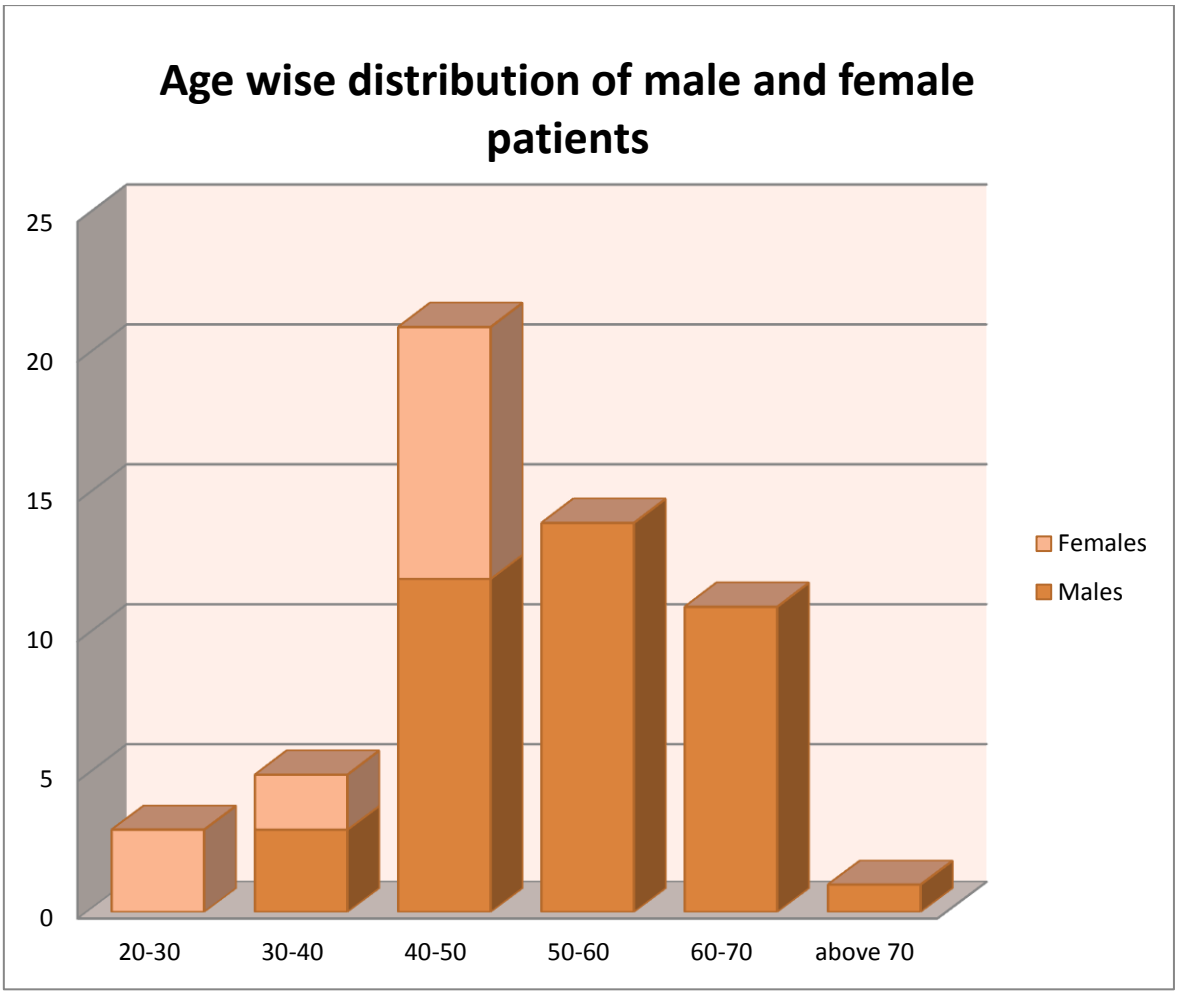


TABLE-8: DISTRIBUTION OF PATIENTS AS PER ETIOLOGY

ETIOLOGY	MALE	FEMALE	TOTAL	%
ALD	19	3	24	40%
HEPATITIS B	17	4	21	38.18%
HEPATITIS C	8	4	12	21.81%

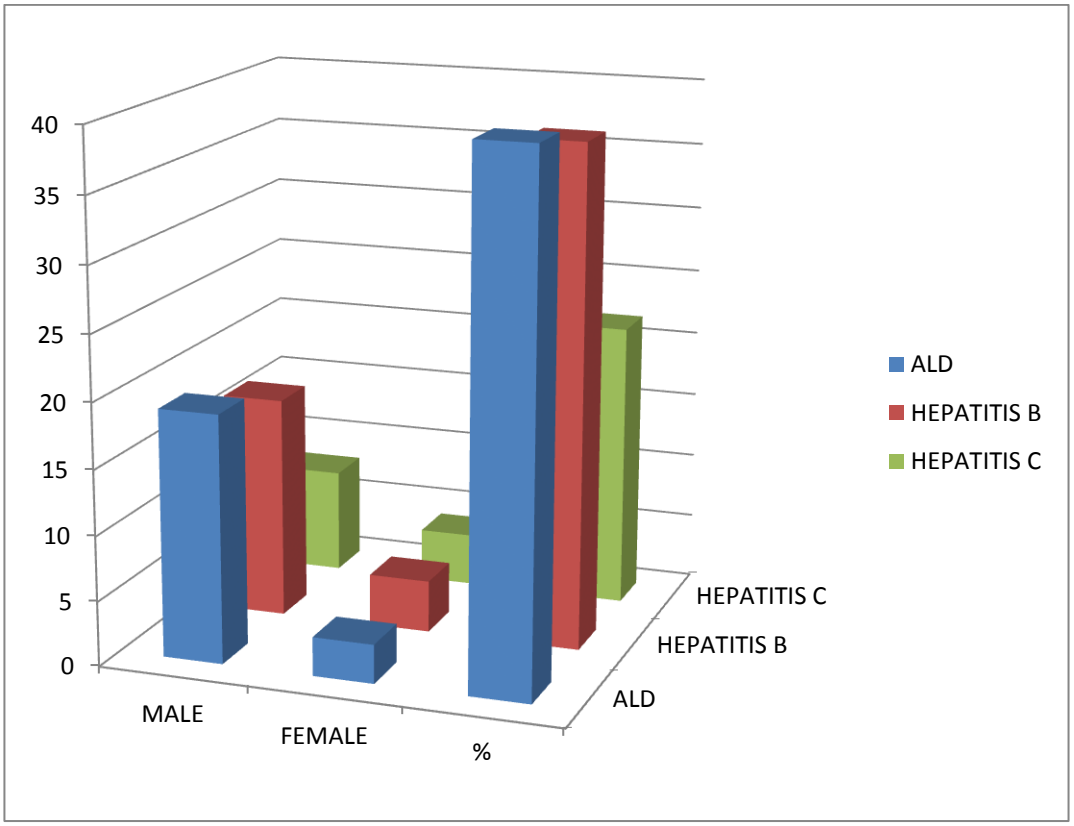
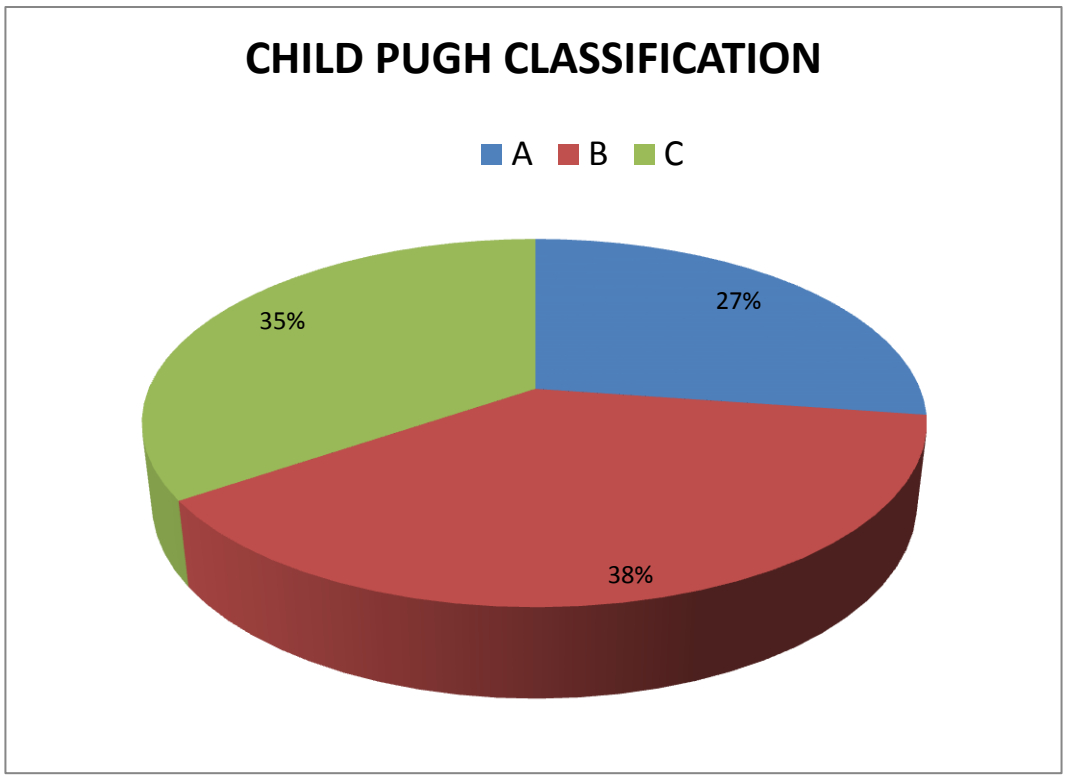


TABLE-9 DISTRIBUTION OF PATIENTS AS PER CHILD PUGH SCORE

CHILD SCORE	TOTAL NUMBER	PERCENTAGE
A	15	27.27%
B	21	38.18%
C	19	34.54%



DEMOGRAPHICS AND CLINICAL PROFILE OF PATIENTS

Age	50.16; 11.79
Gender (Female)	25.45%
Alcoholism	43.63%
Bilirubin	5.16; 4.48
AST	94.35; 59.50
ALT	86.81; 44.91
PT	1.71; 0.58
ALBUMIN	3.34; 0.37
ASCITES	78.18%
CALCIUM	8.97; 0.94

Numbers indicate percentage of cases for dichotomous variables and mean and standard deviation for continuous variables.

PREVALENCE AND RISK FACTORS FOR OSTEOPOROSIS IN CLD

The prevalence of osteoporosis in the study group was 29.09% and the prevalence of osteopenia in the study population was 38.18%. Only 4 out of the 16 patients with osteoporosis had evidence of osteoporosis in their x ray of the lumbosacral spine (23.55%).

Table 6 compares the prevalence of osteoporosis in the alcoholic liver disease group and the post hepatitis group.

	ALD	HEPATITIS	P VALUE
ALL	10(38.46%)	6(20.68%)	0.147*
MALES	8(36.36%)	5(17.24%)	0.490*
FEMALES	2(50%)	1(10%)	0.210*

*Chi square test and Fisher exact t test

The difference in the prevalence of osteoporosis in the Alcoholic liver disease group and in the hepatitis group was statistically insignificant.

UNIVARIATE ANALYSIS OF THE RISK FACTORS ASSOCIATED WITH OSTEOPOROSIS:

1) AGE

Age group	Osteoporosis	Normal	Total
Age<50	8.0(8.964)	21.0(20.036)	29
Age>50	9.0(8.036)	17.0(17.964)	26
Total	17	38	55

Degrees of Freedom = 1

Pearson Chi-Square Statistics = .317

P-Value = 0.5733052076671328

2) SEX

Sex	Osteoporosis	Normal	Total
Male	13.0(11.927)	28.0(29.073)	41
Female	3.0(4.073)	11.0(9.927)	14
Total	16	39	55

Degrees of Freedom = 1

Pearson Chi-Square Statistics = .535

P-Value = 0.46470951095672686

3) TOTAL BILIRUBIN

Results of Two Independent Sample Wilcoxon Rank Sum Test:

BILIRUBIN	OSTEOPOROSIS	NORMAL
SAMPLE SIZE	16	39
MEAN	8.254	3.716

Z score: 3.083

Two sided p value: 0.002

4) ALBUMIN

Results of Two Independent Sample Wilcoxon Rank Sum Test:

ALBUMIN	OSTEOPOROSIS	NORMAL
SAMPLE SIZE	16	39
MEAN	3.106	3.413

Z score: -2.539

Two sided p value: 0.011

5) PROTHROMBIN TIME

Results of Two Independent Sample Wilcoxon Rank Sum Test:

PT/INR	OSTEOPOROSIS	NORMAL
SAMPLE SIZE	16	39
MEAN	2.194	1.508

Z score: 3.456

Two sided p value: 0.001

6) CALCIUM

Results of Two Independent Sample Wilcoxon Rank Sum Test:

CALCIUM	OSTEOPOROSIS	NORMAL
SAMPLE SIZE	16	39
MEAN	9.094	9.208

Z score: 0.454

Two sided p value: 0.650

8) PTH

Results of Two Independent Sample Wilcoxon Rank Sum Test:

PTH	OSTEOPOROSIS	NORMAL
SAMPLE SIZE	16	39
MEAN	55.516	46.229

Z score: 1.835

Two sided p value: 0.067

9) VITAMIN D3

Vitamin D3	Osteoporosis	Normal	Total
Low	14.0(7.564)	12.0(18.436)	26
Normal	2.0(8.436)	27.0(20.564)	29
Total	16	39	55

Degrees of Freedom = 1

Pearson Chi-Square Statistics = 14.649

P-Value = 0.00012

10) CHILD PUGH SCORE

Results of Chi-Square Test for Independent or Homogeneity

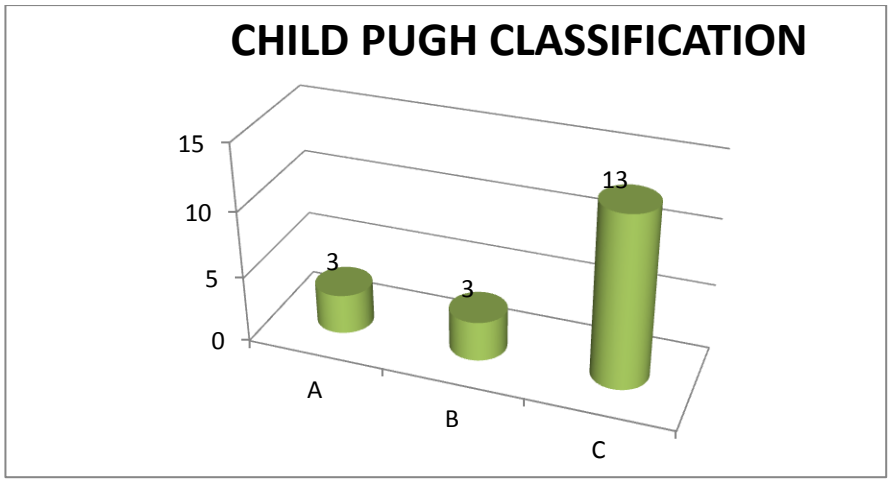
Child Class	Osteoporosis	Normal	Total
A	3.0(4.491)	10.0(8.509)	13
B	3.0(7.600)	19.0(14.400)	22
C	13.0(6.909)	7.0(13.091)	20
Total	19	36	55

Degrees of Freedom = 2

Pearson Chi-Square Statistics = 13.213

P-Value = 0.0013512690533349359

Prevalence of osteoporosis in Child Classes A, B and C



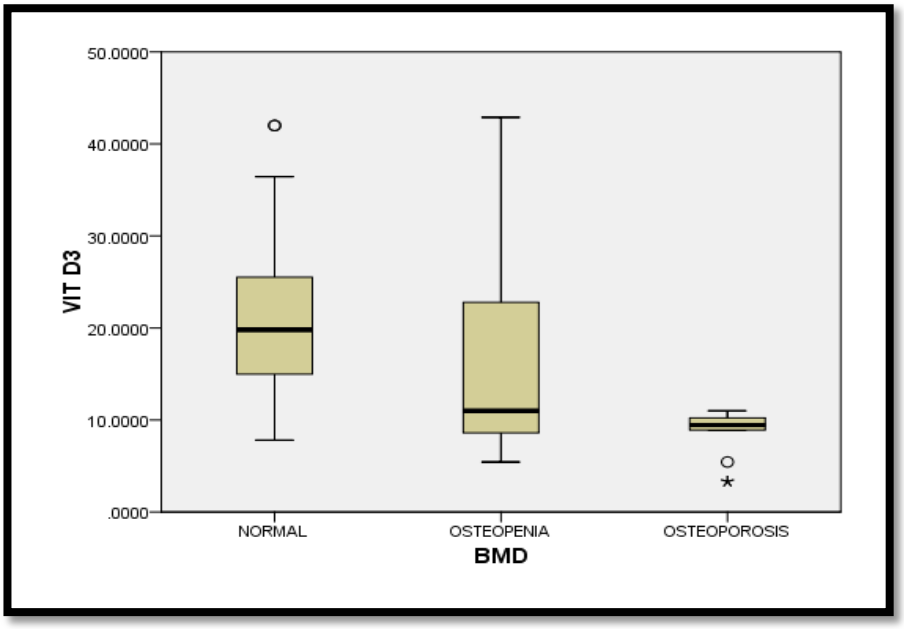


FIGURE: BOX PLOT OF VIT D3 LEVELS IN NORMAL, OSTEOPOROTIC AND OSTEOPENIC INDIVIDUALS.

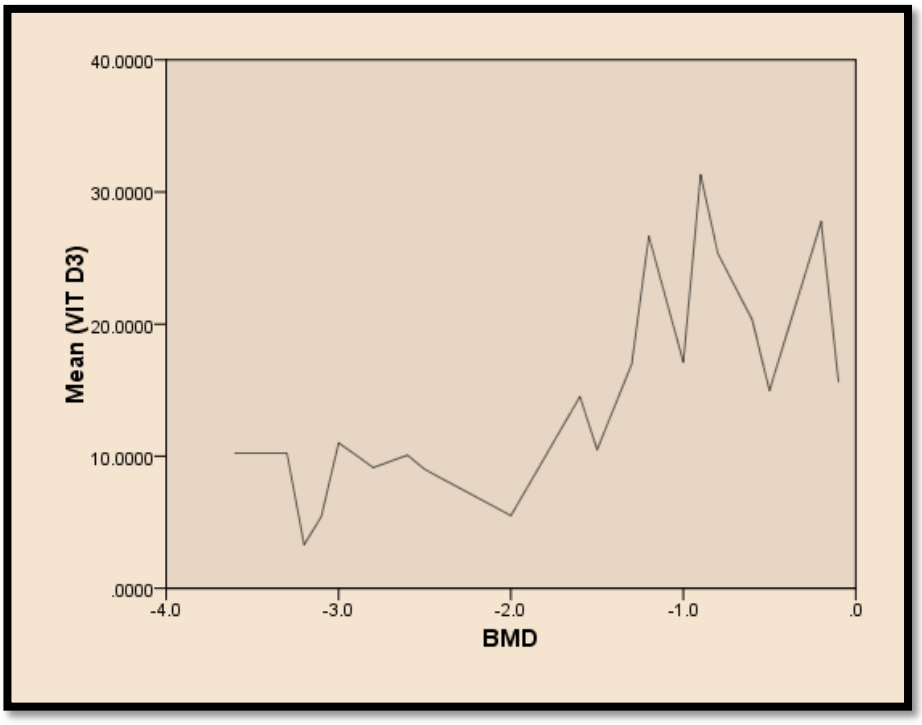


FIGURE 3: VITAMIN D3 LEVELS ACROSS BMD MEASUREMENTS

Logistic Regression analysis was done to find out Independent risk factors for osteoporosis. The results are given in the table below .

Independent risk factors for osteoporosis.

Table 10:

Risk factor	Odds ratio	Confidence interval	p value
Sex	0.473	0.114-1.968	NS
Vitamin D3	16.667	3.28-84.48	0.001
PTH	1.035	0.994-1.077	NS
Bilirubin	1.146	1.001-1.311	0.048
INR	5.136	1.658-15.907	0.005
Albumin	0.508	0.134-1.925	NS
SGOT	1.004	0.992-1.017	NS
Calcium	0.439	0.189-1.018	NS
Phosphorous	1.775	0.796-3.956	NS

For continuous variables the odds ratio indicates the risk of osteoporosis when the magnitude of the variable changes by one standard deviation. For dichotomous variables the odds ratio indicates the risk when the variable changes from 0 to 1. NS=not significant

By logistic regression model it was found that only Vitamin D deficiency , total bilirubin , Prothrombin time and Child class C were independent risk factors for prediction of osteoporosis in decompensated chronic liver disease patients.

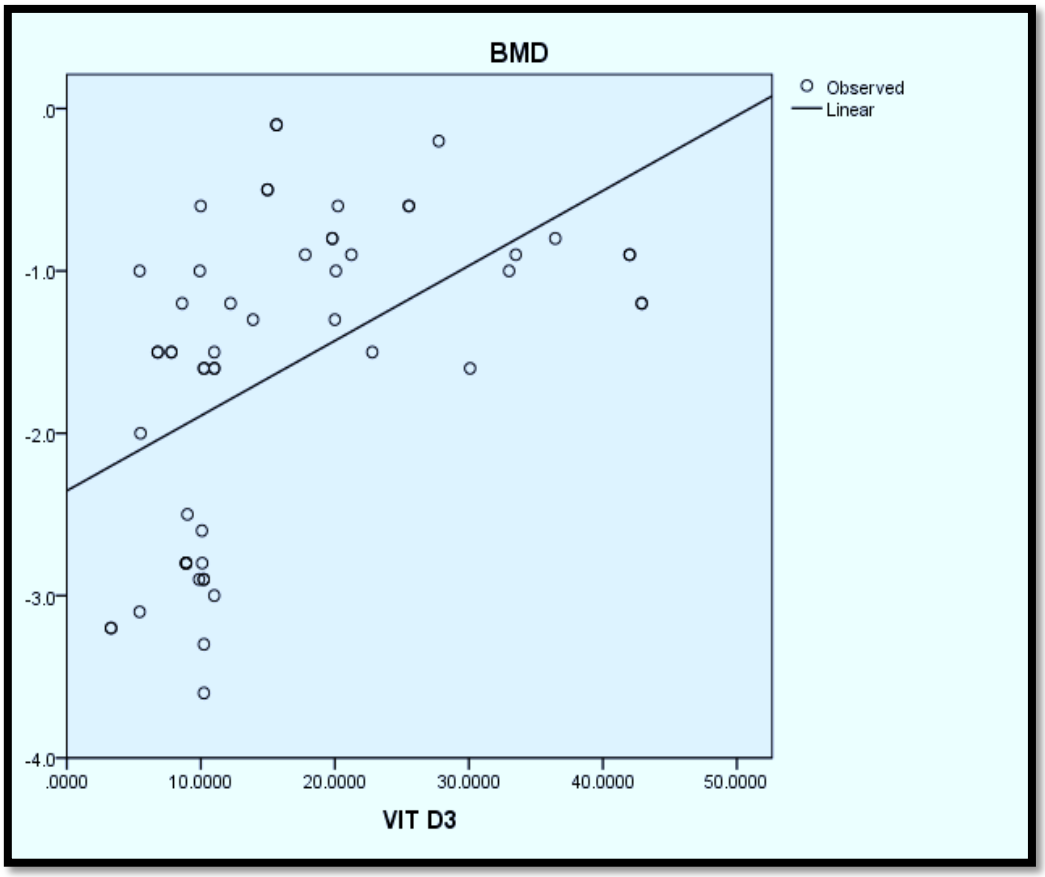


Figure 4: Linear regression curve shows low vitamin D3 levels in the osteoporotic BMD range.

DISCUSSION

DISCUSSION

Osteoporosis is a common condition and the highest incidence rates for osteoporotic fractures are found in the old and in postmenopausal women. The prevalence of osteoporosis is highly dependent upon age and gender. Like Chronic kidney disease liver disease also predisposes to osteoporosis due to numerous causes.

The prevalence of osteoporosis in the cohort was 29.09%, and the prevalence of osteopenia was 38.18%.Only 4 patients had evidence of osteoporosis in their X ray and none of the patients had any fractures. This prevalence is similar to the prevalence in a study done by Ormarsdóttir et al in 72 patients with chronic liver disease of varied etiology[61] . Similarly in a study done by Ghizlane Wariaghli et al. the prevalence of osteoporosis was found to be 43% in a cohort of 64 patients with chronic liver disease (Primary biliary cirrhosis and post hepatitis)[62]. The prevalence among males was 36.36% among ALD group and 17.24% among hepatitis group. The prevalence among females was 50% among ALD group and 10% among hepatitis group. The difference was statistically insignificant.

The difference in the prevalence of osteoporosis in the Alcoholic liver disease group and in the hepatitis group was statistically insignificant.

The size of our patient cohort was limited by several factors. The prevalence of CLD is low in females and our patient cohort was not a randomised sample from the population and included patients admitted in a tertiary care hospital. Only three main causes of Chronic liver disease were included in our study and it included patients with alcoholic liver disease and hepatitis B and hepatitis C. These limitations, however, can also be found in previously published studies. The reported prevalence figures for osteoporosis in patients with CLD range from 9 to 53. These differences in reported prevalence can probably explained by different patient selection factors, different techniques of bone mass measurement and definition of osteoporosis.

We found a high prevalence rate, 65%, in patients classified as Child-Pugh C and only 17% in patients classified as Child Pugh A and B group put together. This association was statistically significant. (P value=0.001). Similar results were obtained in the study by Ormarsdóttir et allfound a high prevalence rate, 42%, in patients classified as Child-Pugh B and C compared with 25% in the Child-Pugh A group.

Increased prothrombin time (as amarker of liver function) was an independent risk factor for osteoporosis. This issupported by other studies that have found the highest prevalence of metabolic bonedisease in patients

with advanced liver disease (25, 31, 41, 46, 54) whereas in earlierstages of liver disease no evidence of bone disease has been found [41, 125].

Apart from belonging to Child-Pugh C and prothrombin time, patients with low 25(OH) VIT D3 levels had the most profound reduction in BMD and 61% of these patients had osteoporosis. Furthermore, in the logistic regression analysis, we found low Vitamin D3 levels to be an independent risk factor for osteoporosis.30% of these patients had osteopenia which is a forerunner of osteoporosis. These findings correlate with the study by Arteh J et al who found Vitamin D deficiency to be universal among patients with Chronic liver disease (92% of patients had vitamin D deficiency and one third of these patients had severe vitamin D- deficiency). In addition to its role in calcium metabolism, vitamin D derivatives may be involved in cell proliferation, differentiation, and immunomodulation [13]. Vitamin D inhibits certain types of matrix metalloproteinases (MMP, a family of zinc-dependent endoproteinases that are involved in degradation of extracellular matrix components) and induces their inhibitors [14]. Consequently, vitamin D deficiency has been associated with increased circulating MMP2,9, a situation that can be corrected with vitamin D supplementation [15]. Other effects of vitamin D include suppression of proliferation of fibroblasts and increased collagen production [16]. These data are relevant to chronic liver disease. Even

though hepatocytes are the major source of MMPs and tissue inhibitors, their production is not affected by the presence of cirrhosis [17]. Therefore, vitamin D deficiency in patients with chronic liver disease (CLD) can lead to progression of hepatic fibrosis. Moreover, inhibition of MMPs has been shown to provide protection from hepatic ischemic injury.

Similarly an association between low albumin levels and osteoporosis was found which was statistically significant (p value 0.011). The mean albumin level among patients with osteoporosis was 3.106 and it was 3.413 among patients without osteoporosis. Similar results are obtained with prolonged prothrombin time.

All other variables like AST, ALT, ALP, Calcium, PTH, PO4 levels were not found to have a statistically significant association with osteoporosis.

By Logistic regression analysis Low Vitamin D3 levels, prolonged prothrombin time, Total bilirubin and Child class C were found to be independent predictors of osteoporosis.

LIMITATIONS OF THE STUDY

The major limitation of our study is small number of subjects we have included in our study and large number of males compared to the females. This is because of the increased prevalence of Chronic liver disease among males. No control arm was available to compare the prevalence of osteoporosis. In DEXA scan only T score was used and not Z score which is based on age and sex matched controls. Being a tertiary care centre, patients with more severe disease are often referred than patients with mild disease. Even though the prevalence of osteoporosis was found out the true incidence of fractures in patients with chronic liver disease is not known and a prospective follow up study is needed to address this issue.

CONCLUSIONS

CONCLUSIONS:

- Chronic Liver disease is a common problem that is associated with increased mortality and poorer health-related quality of life, regardless of the underlying etiology.

- One of the morbidities associated with chronic liver disease is metabolic bone disease.

- The prevalence of osteoporosis is very high among Chronic liver disease patients .29.09% in this study.

- Serum Vitamin D3 levels, Prolonged prothrombin time , Serum albumin levels Child C group (severity of chronic liver disease) and serum bilirubin levels correlated strongly with low BMD levels.

- There was no significant correlation between PTH , serum calcium , age , sex and cause of chronic liver disease with osteoporosis.

- Serum Vitamin D3 levels , Prolonged prothrombin time and severity of chronic liver disease were independent predictors of osteoporosis as per logistic regression analysis.

- Vitamin D deficiency was almost universal and serum levels varied as per the severity of the chronic liver disease.

- Patients with chronic liver disease, should also have BMD performed. BMD measurement is not indicated routinely in other patients with liver disease as there is no evidence at present that osteoporosis is more prevalent in patients who are non-cirrhotic and not cholestatic but further controlled studies are needed.

- Treatment of patients with osteoporosis or those with fragility fractures is a must.

- Treatment options include Bisphosphonates, Calcitriol and Calcitonin.

- Serum 25(OH) Vitamin D3 levels should be measured in all patients with Chronic liver disease and supplementation should be given if found low.

- Vitamin D3 supplementation will retard the progression of chronic liver disease as it inhibits the MMP's and suppresses the proliferation of fibroblasts

- The prevalence of asymptomatic vertebral fractures in patients with chronic liver disease is unknown and needs further study.

RECOMMENDATIONS:

1) Hepatic osteodystrophy should be considered a distinct disease entity in patients with chronic liver disease similar to renal osteodystrophy.

2) BMD and Vitamin D3 should be measured in all patients with decompensated chronic liver diseases.

3) Treatment should be initiated in all patients with osteoporosis or those with fragility fractures.

FUTURE AREAS OF RESEARCH

1) a prospective study of the prevalence of fractures in patients with chronic liver disease;

2) a study of the prevalence of osteoporosis in patients with all stages of PBC compared with sex and age matched controls;

3) a prospective study of the prevalence of hypogonadism in males with cirrhosis with and without osteoporosis;

ANNEXURES

Osteoporosis in Non cholestatic decompensated chronic liver disease and its co-relation with Vitamin D and Parathyroid hormone levels

PROFORMA

Name: Age: Sex: OP.NO:

Address: Ph.No:

Presenting Complaints:

Jaundice: Abdominal distension:

Swelling of legs: Altered sensorium:

Hematemesis: Melena:

Easy fatiguability: Fever:

Purpura/Skin rash: Altered sleep pattern:

Loss of Wt: Loss of Appetite:

Decreased urine output: Dyspnea:

Myalgia: Back pain:

Joint pain:

Abdominal pain:

Drug intake:

Co-morbid Illness: DM: HT: TB: Cardiac illness:

Menstrual h/o: undue bleeding PV:

H/o previous treatment/ surgery/blood transfusion:

H/o high risk sexual behaviour:

others if any:

Personal History:

Alcohol duration: frequency: quantity:

Tobacco Pack years:

EXAMINATION:

Pallor: Jaundice:
Lymphadenopathy: Cyanosis:
Clubbing: Pedal edema:
Others:

PR: BP:

CVS:

RS:

Abdomen:

Genitals:

CNS:

Per rectal / pelvic examination:

INVESTIGATIONS: FOR ALL PATIENTS*:*

CBC

HB%: PCV: ESR:

TC: P: L: E: B: M: Platelets:

RFT: Bl sugar: Urea: Creatinine:

LFT: Tot.bilirubin: Direct: SGOT: SGPT:
Alkaline phosphatase:

Total Protein: Serum Albumin:

PT/INR:

X-RAY CHEST:

X-RAY LS SPINE AND HIP JOINTS:

ECG:

USG-Abdomen:

UGI Scopy:

Viral markers HbsAg: anti-HCV:

Serum Calcium:

Serum phosphorous:

25(OH)Vitamin D3 :

Parathyroid hormone:

DEXA BMD VALUE OF LUMBAR SPINE:

CHILD SCORE : A/B/C

PARAMETER	1	2	3
Ascites	absent	Slight	moderate
Hepatic encephalopathy	none	Grade 1-2	Grade3-4
Bilirubin	<2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
PT Secs over control INR	 <4 <1.7	 4-6 1.7-2.3	 >6 >2.3
A:5-6 B:7-9 C:10-15			

INVESTIGATIONS: IN SELECTED PATIENTS

Liver biopsy:

FINAL ETIOLOGY :

DISEASE SEVERITY:

BMD SCORE OF LUMBAR SPINE:

VITAMIN D AND PTH STATUS :

PATIENT CONSENT FORM

Study detail: Osteoporosis in Non cholestatic decompensated chronic liver disease and its co-relation with Vitamin D and Parathyroid hormone levels

Study centre : Institute of Internal Medicine, Madras Medical College, Chennai.

Patients Name :

Patients Age :

Identification Number :

Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patients Name and Address: place date

Signature of investigator :

Study investigator's Name : place date

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INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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CERTIFICATE OF APPROVAL

To
Dr. Anandan S.P.S
PG in MD General Medicine
Institute of Internal Medicine
Madras Medical College , Chennai -3

Dear Dr. Anandan S.P.S

The Institutional Ethical Committee of Madras Medical College reviewed and discussed your application for approval of the project / proposal entitled " Osteoporosis is Non cholestatic decompensated chronic liver disease and its co-relation with Vitamin D and Parathyroid hormone levels" No. 020610

The following members of Ethical committee were present in the meeting held on 11.06.2010 conducted at Madras Medical College,

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. J. Mohanasundaram, MD,Ph.D,DNB Dean, Madras Medical College, Chennai -3	-- Deputy Chairman
3.	Prof. A. Sundaram, MD Vice Principal , MMC, Chennai -3	-- Member Secretary
4.	Prof. R. Sathianathan, MD Director, Institute of Psychiatry	-- Member
5.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
6.	Prof. Pregna B. Dolia , MD Director, Institute of Biochemistry, MMC, Ch-3	-- Member
7.	Prof. C. Rajendran , MD Director, Institute of Internal Medicine, MMC, Ch-3	-- Member -- Member
8.	Prof. Geetha Subramanian, MD,DM Professor & Head , Dept. Of Cardiology	-- Member
9.	Prof. V. Shruti Kamal, MS Professor of Surgery, MMC, Ch-3	-- Member
10.	Prof. Md. Ali, MD, DM Professor & HOD of Medical Gastroenterology, MMC,	-- Member -- Member
11.	Tmt. Arnold Souline	-- Social Scientist

We approve the trail to be conducted in its presented form.

Sd/. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patien information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee.

S.NO	NAME	AGE	SEX	ALCOHOL	DRUG INT	ASCITES	PEDAL ED	HEP ENCE	UGI BLEED
1	KAMALAKANNAN	45	m	yes	no	yes	yes	no	no
2	GURUNATHAN	70	m	no	no	yes	no	no	no
3	SELVI	25	f	no	no	yes	yes	no	yes
4	DURAISAMY	44	m	yes	no	no	no	no	no
5	PITCHAI	52	m	yes	no	yes	yes	yes	yes
6	VEERARAGHAVAN	45	m	yes	no	yes	yes	yes	yes
7	SELVARAJ	62	m	yes	no	yes	no	no	no
8	VENDA	36	f	no	no	no	no	no	no
9	HARIDAS	68	m	no	no	yes	yes	no	no
10	JOSEPH	70	m	yes	no	yes	yes	no	yes
11	PALANIAPPAN	54	m	yes	no	yes	yes	no	no
12	KUMAR	52	m	yes	no	yes	yes	no	yes
13	RAJENDRAN	34	m	yes	no	yes	yes	no	yes
14	SAROJA	30	f	yes	no	yes	yes	no	no
15	MANIKANDAN	78	m	yes	no	yes	yes	yes	yes
16	SWAMINATHAN	57	m	no	no	yes	yes	no	no
17	GOPAL	45	m	yes	no	no	no	no	no
18	NARAYANAN	62	m	yes	no	no	no	no	no
19	ARAVINDAN	60	m	yes	no	yes	yes	no	yes
20	GOPAL	39	m	no	no	yes	yes	no	no
21	RAMESH	40	m	no	no	yes	yes	no	yes
22	SURYA NARAYANAN	43	m	no	no	yes	yes	no	no
23	DEENADAYALAN	56	m	yes	no	yes	yes	no	yes
24	SAMINATHAN	58	m	yes	no	yes	yes	yes	yes
25	MURUGAN	59	m	yes	no	yes	yes	yes	yes
26	MALLIGA	26	f	no	no	yes	no	no	no
27	GANESAN	66	m	no	no	yes	no	no	no
28	THAMBIDURAI	56	m	yes	no	yes	yes	yes	no
29	RAJAN	50	m	no	no	yes	yes	no	no
30	PENCILLIAH	58	m	yes	no	yes	yes	no	no
31	KARPAGAM	49	f	yes	no	yes	yes	no	yes
32	SELVI	48	f	no	no	no	no	no	no

T.B	D.B	SGOT	SGPT	ALP	T.P	ALBUMIN	SUGAR	UREA	CREAT	HB	TC
3.4	2	84	98	120	6.6	3.2	98	32	1.1	9	4000
0.7	0.2	31	41	76	6.7	3.5	82	31	1.1	7	6400
1.2	0.3	70	87	145	6	2.6	123	40	1.3	8	4500
2.4	1	143	200	240	6.4	3.6	100	24	1	9.8	7600
12.6	5.6	124	223	256	6	2.9	60	40	1.5	7.3	11800
17.8	7.8	80	89	120	6	2.8	56	32	1.3	9.8	10000
0.7	0.2	45	43	112	6.8	3.5	76	21	1	10.2	3400
2.4	1	132	123	146	6.5	4.4	98	16	1.1	11	4000
3.4	1.4	72	78	132	6.2	3.8	122	26	1.2	10.5	5400
10.4	6.7	46	31	76	6	3.1	55	36	1.3	9.9	3200
2.1	1.2	43	40	67	6.6	2.9	56	22	1	9.8	10900
1.2	0.4	92	99	120	6	3.5	67	31	1.3	10.2	9700
0.8	0.1	149	99	56	5.4	4.3	81	29	0.8	11	2500
5.6	3.2	31	31	88	5.9	3.2	93	26	0.7	9.9	3200
11.8	3.5	77	67	99	6.7	2.7	67	40	1.2	7.8	6000
3.2	1.4	42	40	98	6.4	3.2	78	21	1	12	7600
3.6	2.2	200	189	231	6	3.3	98	34	0.9	11	6100
4.3	1.2	67	76	112	6.8	3.3	89	31	1	12	7890
4.5	2	44	45	99	6.3	3	45	27	1.3	9	3500
0.9	0.2	99	124	145	6.7	3.3	78	12	0.6	12	8900
4.7	1.8	34	31	110	6	2.8	78	22	1.1	9.8	2400
3.4	1.4	72	78	132	6.2	3.8	122	26	1.2	10.5	5400
11.2	8.9	56	67	91	6.9	3.5	87	30	1.1	9.2	3900
13.6	5.6	124	223	256	6	3	60	40	1.5	6.3	11800
10.8	5.6	124	223	256	6	3	60	40	1.5	5.3	11800
0.9	0.2	44	40	111	6.2	3.8	89	31	0.7	11.2	6100
1.9	0.7	56	45	120	6.6	3.6	67	21	0.9	12	7390
11	5.8	78	91	78	6	2.9	60	34	1.3	9	3100
10.9	4.7	45	46	100	6.4	3.1	84	28	0.9	10	4500
0.9	0.2	42	47	120	6.9	3.7	89	31	1.1	13	5600
11.2	6.7	46	45	76	6	3	99	30	1.2	9.9	7700
2.4	1	132	123	146	6.5	4.1	98	16	1.1	11	4000

PLT	ESR	INR	POR DOP	CXR	XRAY LS‖	USG	UGIS
4	34	2.5	PHT	N	N	CLD	GRADE 1 varices
1.52	62	1.2	PHT	N	N	CLD	GRADE 1 Varices
1.1	30	1.5	PHT	N	N	CLD	GRADE 3 Varices
3.5	20	1	NO	N	N	CLD	GASTRIC EROSIONS
1.2	46	2.8	PHT	PLEU EFF	N	CLD	GRADE 3 Varices
2.5	32	2.5	PHT	PLEU EFF	N	CLD	GRADE 3 Varices
0.9	12	1.5	PHT	PLEU EFF	N	CLD	N
3.5	10	1	NO	N	N	CLD	N
1.5	30	1.6	PHT	N	N	CLD	GRADE 1 Varices
1.4	42	2.1	PHT	PLEU EFF	OSTEOPOROTIC	CLD	GRADE 3 Varices
4.2	30	1.6	PHT	N	N	CLD	N
2.6	30	1.2	PHT	N	N	CLD	GRADE 3 Varices
1	30	1.5	PHT	N	N	CLD	GRADE 1 Varices
0.8	30	2	PHT	N	N	CLD	GASTRIC EROSIONS
1	23	3	PHT	PLEU EFF	OSTEOPOROTIC	CLD	GRADE 3 Varices
1.8	12	1.2	PHT	N	N	CLD	PROMINENT VEINS
2.3	20	1	PHT	N	N	CLD	N
3.3	11	1.2	PHT	N	N	CLD	N
3.7	22	2.1	PHT	PLEU EFF	OSTEOPOROTIC	CLD	GRADE 3 Varices
1.6	17	1.4	PHT	N	N	CLD	N
1.2	36	1.9	PHT	N	N	CLD	PROMINENT VEINS
3.9	30	1.6	PHT	N	N	CLD	GRADE 1 Varices
0.9	21	2	PHT	N	N	CLD	GRADE 2 VARICES
1.2	46	2.8	PHT	PLEU EFF	N	CLD	GRADE 3 Varices
1.2	46	2.8	PHT	PLEU EFF	N	CLD	GRADE 3 Varices
1.7	19	1	PHT	N	N	CLD	NORMAL
3.8	10	1	PHT	N	N	CLD	PROMINENT VEINS
0.9	29	2.6	PHT	N	N	CLD	GRADE 3 Varices
1.2	10	1.8	PHT	N	N	CLD	GRADE 1 Varices
1.9	14	1.6	PHT	N	N	CLD	GRADE 1 Varices
4.4	12	1.8	PHT	PLEU EFF	N	CLD	GRADE 2 VARICES
3.5	10	1	NO	N	N	CLD	N

HBsAG	anti HCV	CAL	PO4	VIT D3	PTH	BMD	CHILD'S	DIAGNOSIS	ANA
neg	neg	9.8	3	10.1	39.46	-2.8	C	ALD	NA
neg	positive	9	4	22.79	39.46	-1.5	B	HEP C CLD	NA
neg	positive	10	3	36.45	42	-0.8	B	HEP C	NA
neg	neg	9.6	3.2	20.23	33.5	-0.6	A	ALD	NA
neg	neg	9	4.5	8.9	70	-2.8	C	ALD	NA
neg	neg	9.2	3.3	20	65	-1.3	C	ALD	NA
neg	neg	9.1	3.6	33.5	42	-0.9	A	ALD	NA
neg	positive	9.1	3.8	42	60.06	-0.9	A	HEP C	NEG
pos	NEG	9	4	10.23	65	-3.3	B	HEP B	NA
neg	neg	9.1	4.3	11	56	-3	C	ALD	NA
neg	neg	8.9	2.3	33	43.22	-1	B	ALD	NA
neg	neg	8	3.1	9.99	26	-0.6	B	ALD	NA
neg	neg	7.9	4	42.9	59.12	-1.2	B	ALD	NA
neg	neg	10	2	30.09	77	-1.6	C	ALD	NA
pos	neg	8.9	3.5	3.3	80	-3.2	C	HEP B ,ALD	NA
neg	positive	9.1	3.3	15.65	45.22	-0.1	A	HEP C	NA
neg	neg	10.9	2.1	25.52	41.11	-0.6	A	ALD	NA
neg	neg	11	3.3	20.08	40.32	-1	A	ALD	NA
neg	neg	9.2	4.1	9	55.5	-2.5	C	ALD	NA
pos	neg	9.8	2.5	10.21	33.33	-2.9	A	HEP B	NA
pos	neg	9.8	3.5	14.97	42.19	-0.5	C	HEP B	NA
pos	neg	9	4	10.23	65	-3.6	B	HEP B	NA
neg	neg	9.1	3.4	8.6	45	-1.2	C	ALD	NA
neg	neg	8.8	4.5	8.9	45	-2.8	C	ALD	NA
neg	neg	9.2	4.5	8.9	46	-2.8	C	ALD	NA
pos	neg	10.3	2.1	27.75	41	-0.2	A	HEP B	NA
pos	neg	9.2	2.8	11	35.76	-1.5	A	HEP B	NA
neg	neg	8.7	4.3	9.87	56.64	-2.9	C	ALD	NA
neg	positive	8.7	3.8	13.89	61.1	-1.3	B	HEP C	NA
neg	neg	9.8	3.6	21.23	34.45	-0.9	A	ALD	NA
neg	neg	9.3	4.3	10.08	56	-2.6	C	ALD	NA
neg	positive	9.1	3.8	42	60.06	-0.9	A	HEP C	NA

ANTI LKM	AMA	SMA	CERULOP	LIVER BIO	VITD STAT	BMD
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	OSTEOPENIA
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	NORMAL
NEG	NEG	NEG	NA	CIRRHOSIS	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	NORMAL
NA	NA	NA	NA	ND	N	OSTEOPENIA
NA	NA	NA	NA	ND	N	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	OSTEOPENIA
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	CIRRHOSIS	N	NORMAL

33	DEVANATHAN	47	m	no	no	yes	yes	no	no
34	SIVAKUMAR	65	m	no	no	yes	yes	no	yes
35	SUBRAMANI	63	m	no	no	no	no	no	yes
36	PARVATHI	41	f	yes	no	yes	yes	no	no
37	MAHESWARI	47	f	no	no	yes	yes	no	no
38	CHENGAMMAL	43	f	no	no	no	no	no	yes
39	CHENNIAPPAN	61	m	yes	no	yes	yes	no	no
40	FRANCIS	47	m	yes	no	no	no	no	yes
41	MOHAMMED BASHA	43	m	no	no	no	no	no	yes
42	RAJAIAH	49	m	no	no	yes	yes	no	no
43	XAVIER	47	m	yes	no	yes	yes	no	no
44	JANANATHAN	54	m	no	no	yes	yes	yes	yes
45	GURUSAMY	53	m	yes	no	yes	yes	yes	yes
46	KUMAR	59	m	yes	no	yes	no	no	yes
47	KARTHIKEYAN	50	m	yes	no	yes	yes	yes	yes
48	BABU	60	m	no	no	yes	yes	no	no
49	THULASIAMMAL	33	f	no	no	no	no	no	no
50	SIVAKAMI	42	f	no	no	yes	yes	no	no
51	MANI	65	m	no	no	yes	yes	no	yes
52	LOGANATHAN	63	m	no	no	no	no	no	yes
53	CHELLAMMAL	41	f	yes	no	yes	yes	no	no
54	NAZEER BEGUM	47	f	no	no	yes	yes	no	no
55	MARIAMMAL	43	f	no	no	no	no	no	yes

3.4	1.4	72	78	132	6.2	3.8	122	23	1.2	10.5	5400
0.9	0.3	103	112	390	5.7	2.8	66	20	0.9	11	4200
4.8	2.1	43	32	142	6.9	3.7	98	32	0.8	10	3400
0.9	0.3	78	87	121	6.8	3.3	67	24	0.9	11	7200
3.2	1.6	120	132	99	6.2	2.9	86	18	1.1	12	1900
7.8	2.2	150	200	180	6.3	3.7	54	32	1.3	9.8	9800
5.9	3.2	76	67	99	6.7	3.6	140	11	1	6.7	1800
9.6	5.4	89	78	100	6	2.8	109	17	1.1	5	2500
3.6	2.2	200	189	231	6	3.3	56	32	1.3	9.8	10000
4.3	1.2	67	76	112	6.8	3.3	76	21	1	10.2	3400
4.5	2	44	45	99	6.3	3	98	16	1.1	11	4000
0.8	0.1	149	99	56	5.4	4.2	81	29	0.8	11	2500
12.2	5.6	124	223	256	6	2.9	60	40	1.5	7.3	11800
2.1	1	77	80	100	6.8	4	80	12	0.8	10.5	10000
11.6	3.5	77	67	99	6.7	3.6	67	40	1.2	7.8	6000
3.2	1.4	42	40	98	6.4	3.2	78	21	1	12	7600
3.6	2.2	200	189	231	6	3.3	98	34	0.9	11	6100
1.2	0.4	46	48	110	6.7	3.8	112	26	1.2	13	5600
0.9	0.3	103	112	390	5.7	2.8	66	20	0.9	11	4200
4.8	2.1	43	32	142	6.9	3.7	98	32	0.8	10	3400
0.9	0.3	78	87	121	6.8	3.3	67	24	0.9	11	7200
3.2	1.6	120	132	99	6.2	4.2	86	18	1.1	12	1900
7.8	2.2	150	200	180	6.3	3.7	54	32	1.3	9.8	9800

1.5	30	1.6	PHT	N	N		CLD	GRADE 1 Varices
1.23	12	1.4	PHT	PLEU EFF	N		CLD	GRADE 1 Varices
2.45	30	2	PHT	N	N		CLD	GRADE 2 VARICES
4	23	1	PHT	N	N		CLD	N
1.1	12	1.2	PHT	N	N		CLD	N
3.2	29	2	PHT	N	N		CLD	GASTRIC EROSIONS
0.6	26	2.2	PHT	N	N		CLD	GRADE 1 Varices
0.89	30	1.7	PHT	N	N		CLD	GRADE 2 VARICES
2.5	17	1.4	PHT	N	N		CLD	N
0.9	36	1.9	PHT	N	N		CLD	PROMINENT VEINS
3.5	30	1.6	PHT	N	N		CLD	GRADE 1 Varices
1	30	1.5	PHT	N	N		CLD	GRADE 1 Varices
1.2	46	2.8	PHT	PLEU EFF	N		CLD	GRADE 3 Varices
2.2	20	1.8	PHT	N	N		CLD	GASTRIC EROSIONS
1	23	3	PHT	PLEU EFF	OSTEOPOROTIC		CLD	GRADE 3 Varices
1.8	12	1.2	PHT	N	N		CLD	PROMINENT VEINS
2.3	20	1	PHT	N	N		CLD	N
3.2	28	1.4	PHT	N	N		CLD	N
1.23	12	1.4	PHT	PLEU EFF	N		CLD	GRADE 1 Varices
2.45	30	2	PHT	N	N		CLD	GRADE 2 VARICES
4	23	1	PHT	N	N		CLD	N
1.1	12	1.2	PHT	N	N		CLD	N
3.2	29	2	PHT	N	N		CLD	GASTRIC EROSIONS

pos	neg	10	4	10.23	65	-1.6	B	HEP B	NA
pos	neg	9.5	2.8	11	55	-1.6	B	HEP B	NA
neg	positive	8.7	2.5	6.78	57	-1.5	B	HEP C	NA
neg	neg	7.8	4	5.43	31	-1	B	ALD	NA
neg	positive	9.2	3.8	19.81	24.42	-0.8	B	HEP C	NA
pos	neg	9.9	4.2	7.8	26.78	-1.5	B	HEP B	NA
neg	neg	9.2	4.1	9.92	63	-1	B	ALD	NA
neg	neg	11	4.5	17.79	31.12	-0.9	C	ALD	NA
pos	neg	9.8	2.5	10.21	33.33	-2.9	A	HEP B	NA
pos	neg	9.8	3.5	14.97	42.19	-0.5	C	HEP B	NA
pos	neg	9.1	4	10.23	65	-1.6	B	HEP B	NA
pos	neg	8.9	4	42.9	59.12	-1.2	B	HEP B	NA
neg	neg	8	4.5	8.9	70	-2.8	C	ALD	NA
neg	neg	7.6	3.3	5.5	60	-2	B	ALD	NA
pos	neg	8.1	3.5	3.3	80	-3.2	C	HEP B ,ALD	NA
neg	positive	9.1	3.3	15.65	45.22	-0.1	A	HEP C	NA
neg	neg	10.9	2.1	25.52	41.11	-0.6	A	ALD	NA
neg	positive	11.2	5.6	12.21	36.9	-1.2	A	HEP C	NA
pos	neg	9.5	2.8	11	55	-1.6	B	HEP B	NA
neg	positive	8.7	2.5	6.78	57	-1.5	B	HEP C	NA
neg	neg	9.4	4	5.43	31	-3.1	C	ALD	NA
neg	positive	9.2	3.8	19.81	24.42	-0.8	B	HEP C	NA
pos	neg	9.9	4.2	7.8	26.78	-1.5	B	HEP B	NA

NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	N	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPENIA
NA	NA	NA	NA	ND	LOW	OSTEOPOROSIS
NA	NA	NA	NA	ND	N	NORMAL
NA	NA	NA	NA	ND	N	NORMAL